Instrument for the non-invasive evaluation of human arterial endothelial function via measurement of changes in the transit time of an artificial pulse

Jonathan S Maltz, Thomas F. Budinger [1]
Department of Functional Imaging, Lawrence Berkeley National Laboratory
Department of Bioengineering, University of California, Berkeley

Abstract- Impairment of arterial endothelial function is an early event in atherosclerosis and correlates with the major risk factors for cardiovascular disease. The most widely used non-invasive measure of endothelial function involves the brachial artery (BA) diameter measurement using ultrasound imaging before and after several minutes of blood flow occlusion. The change in arterial diameter is a measure of flow-mediated vasorelaxation (FMVR). The high variability of results and high cost of instrumentation render this technique unsuitable for routine clinical use. We present an instrument we call the "relaxoscope" that is designed to overcome many obstacles that confine non-invasive assessment of FMVR to research settings. The relaxoscope induces an artificial pulse at the superficial radial artery via a linear actuator. An ultrasonic Doppler stethoscope detects this pulse 10-20 cm proximal to the point of pulse induction. The delay between pulse application and detection provides the pulse transit time (PTT). By measuring PTT before and after 5 minutes of BA occlusion and ensuing reactive hyperemia, FMVR may be measured based on the changes in PTT caused by changes in vessel caliber, smooth muscle tone and wall thickness. We compare the results obtained using the relaxoscope with M-mode BA diameter measurements in human subjects.

Keywords- endothelial function, pulse wave velocity, pulse transit time, flow-mediated dilation

I. INTRODUCTION

Endothelial dysfunction is an important initial event in atherogenesis [1, 2, 3, 4, 5] and is strongly correlated with all the major risk factors for cardiovascular disease (CVD) [6, 7, 8, 9]. In addition, it is one of the earliest predictors of CVD [6, 10] and coronary events [11]. Also, factors that are considered beneficial for cardiovascular health, such as exercise [12], appear to improve endothelial function [13]. The fact that no assessment of endothelial function is included as part of the routine medical examination constitutes a major deficit of current clinical practice, given the extremely high incidence of CVD among the population of the Western world.

The most common method for the assessment of endothelial function is the measurement of the diameter of the brachial artery using high-resolution ultrasound before and after an arterial occlusion of several minutes duration. The reactive hyperemic flow that ensues once the occlusion is removed stimulates endothelial cells to release chemical factors that relax the surrounding vascular smooth muscle. The change in arterial caliber effected by this mechanism is termed flow-mediated vasodilation (FMD). The coefficients of variation of the FMD measurements obtained using the ultrasound imaging method vary widely from as little as 1.5% in a few studies to approximately 50% in many others [14, 15, 16, 17]. Some investigators have considered FMD values of less than 5% as indicative of endothelial dysfunction (ED), while others have observed mean FMDs of more than 5% in cardiovascular disease states. These statistics suggest that this method of measuring FMD is too sensitive to differences in methodology to allow its routine use in a clinical setting.

We present a new instrument, which we refer to as the "vascular relaxoscope", for the non-invasive assessment of flow-mediated vasorelaxation (FMVR), which theoretically provides a more sensitive measure of endothelium-mediated vasomotion than do methods that measure FMD. The relaxoscope measures vasorelaxation via the effect of this process on the transit time of an artifical pulse through a segment of an artery. Figure 1 illustrates this schematically.

Many techniques for PTT and PWV measurement have been presented in the past [18, p. 102-106]. Most rely on calculating the time delay between the rising edges of individual natural pulse pressure or flow waves as they pass two points along the propagation path. Non-linear viscoelastic properties of arterial walls introduce dispersion: different frequency components of the pulse or flow wave travel at different speeds. Also, pulse pressure affects transit speed. Both of these factors lead to the high variability of the measurements obtained.

Anliker et al. studied the canine aorta by introducing artificial pulse waves through insertion of a vibrating device within the artery. Traveling waves were detected using an intra-arterial pressure transducer. Measurements characterized by greater accuracy and repeatability than those derived from the natural pulse wave were obtained [19]. This may be attributed to the well-defined nature, and low amplitude of the induced pulses. Landowne performed similar invasive measurements in the human forearm. An armature within a solenoid delivered mechanical pulses to the radial artery, and resultant pressure waves were measured proximal to the site of administration using an intra-arterial

[1]This work was supported in part by the National Heart, Lung, and Blood Institute of the U.S. Department of Health and Human Services under grants HL-07367, R01-HL50663 and P01-HL25840, in part by the National Institute on Aging grant AG-05890, and in part by the Director, Office of Science, Office of Biological and Environmental Research, Medical Sciences Division of the U.S. Department of Energy under contract DE-AC03-76SF00098.

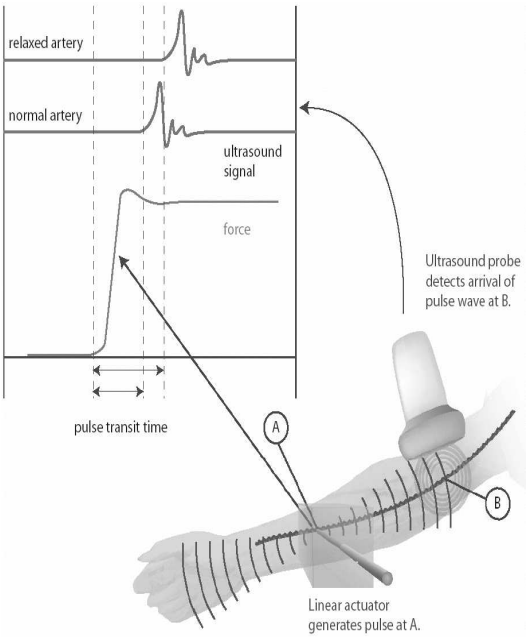

Figure 1: The transit time of an artifi cial pulse is dependent on the state of relaxation of the arterial wall. The relaxoscope measures this PTT.

catheter transducer [20]. The relaxoscope, which we now describe, performs this measurement non-invasively.

II. Instrument design

The current prototype of the relaxoscope appears in Figure 2. The instrument employs a force-feedback controlled linear motor (Baldor Electric Co., Fort Smith, AR), the actuating stem of which makes contact with the skin to introduce an artificial pulse at the superficial segment of the radial artery. An applanation tonometer (Millar Instruments Inc., Houston TX) at the free end of the stem senses the applied force. This allows for closed-loop control of the force waveform and accommodates different lateral positions of the wrist of the subject. An analog PID controller is employed for this purpose.

Several centimeters proximal to the site of pulse introduction, an 8 MHz continuous wave Doppler ultrasonic stethoscope records the incident flow waves produced by these pulses. In this way, the arterial pulse transit time (PTT) is measured, and the pulse wave velocity (PWV) estimated when the distance between the actuator and and ultrasonic sensor is known. PTT measurements are taken during diastole when interference between natural and induced pulses is least significant.

By applying a constant force input signal, the relaxoscope can be used to conveniently acquire the pulse pressure waveform of the subject.

The relaxoscope includes actuator rate limiting as a safety feature. Actuator position is measured using a linear variable differential transformer mounted on the motor armature. An analog differentiator and comparator limit the maximum speed of the armature.

The force input, motor control, ultrasound audio, force applied and position signals are simultaneously recorded using a multifunction data acquisition card (NI-PCI 6035E, National Instruments Corp, Austin TX) at a sampling rate of 10kHz per channel.

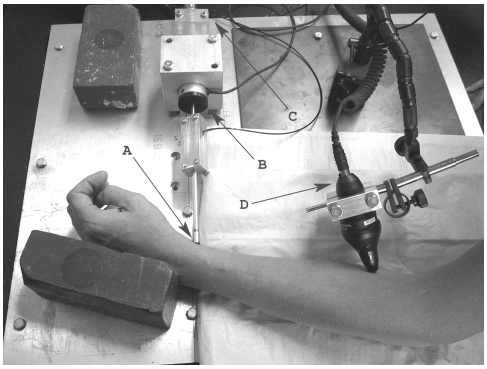

Figure 2: A subject's arm is shown positioned on the relaxoscope platform. The artifi cial pulse is applied by the force-sensing actuator stem tip at (A). The stem is driven by linear motor (B) and actuator displacement is measured using linear variable differential transformer (C). Induced fbw velocities are recorded using Doppler stethoscope (D).

At present, PTT measurements are obtained manually by marking the rising edge of the induced force pulse (applied at point A in Figure 2) and the first flow signal corresponding to the arrival of the artificial pulse at the ultrasonic transducer (D). A typical set of acquired waveforms is shown in Figure 3.

III. Evaluation of arterial endothelial function

To determine how vasorelaxation can be measured via PTT, we refer to the Moens-Korteweg equation, which describes with reasonable accuracy the relationship between PWV and arterial dimensions and material properties:

$$\frac{1}{\text{PTT}} = c = \sqrt{\frac{Eh}{2\rho R}} \tag{1}$$

where c is the PWV, E is the Young's modulus of the arterial wall, h is the wall thickness, ρ is the blood density and R represents the arterial radius [21, p. 91]. As R increases owing to endothelium-mediated smooth muscle relaxation, the PWV decreases. Also, relaxation of vascular smooth muscle reduces E and the wall thickness h, and hence c [18, p. 100-101]. Thus, the greater the drop in PWV between preocclusion and postocclusion measurements, the more robust the endothelium-mediated dilation response.

IV. Preliminary evaluation of the relaxoscope in human subjects

The relaxoscope is currently undergoing a preliminary evaluation in which measurements of reactive hyperemia-

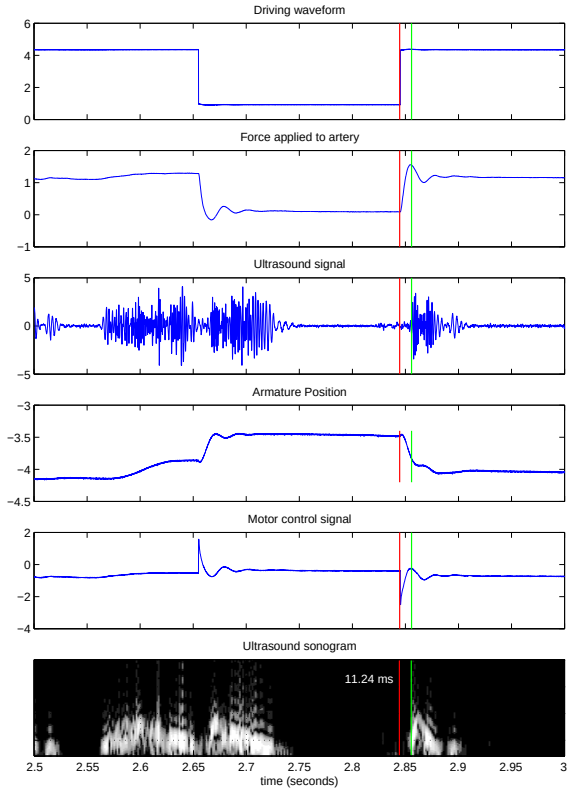

Figure 3: The five recorded waveforms from the relaxoscope are plotted here versus time. The first plot shows the force control input which is a 3 Hz square-wave. A controller produces a control signal that is amplified and fed to the motor (fifth plot), so that the force applied to the radial artery (second plot) tracks the control input. As soon as the force waveform rises, the actuator tip is exerting pressure on the artery. The induced pulse travels through the artery, and the rising (earliest arriving) signal is shown in the third plot of the Doppler ultrasound signal at the stethoscope. The rising edge of the force pulse and that of the ultrasound signal are marked, and a delay of 11.24 ms is calculated. Note the natural pulse signal that occurs between 2.55 and 2.75 seconds. It is coincident with the artificial pulse induced as the actuator withdrew on the previous cycle of the control input waveform. The sixth plot is the sonogram of the ultrasound signal

induced changes in PTT (assumed to correlate with flow-mediated vasorelaxation and hence FMD) are compared to results obtained using the present gold standard: measurements of pre- and posthyperemic arterial diameter variation derived from B-mode images and/or M-mode arterial wall echo-tracking data. The evaluation protocol, consists of two procedures. Procedure A involves evaluation of flow-mediated vasorelaxation (FMVR) in the left arm of subjects, while Procedure B consists of a standard FMD assessment in the right arm. Both procedures utilize a 5 minute occlusion of the brachial artery in order to induce reactive hyperemia.

The two procedures are carried out sequentially in random order on the same individual. Procedures A and B are performed with a maximum interval of one hour between the procedures.

Procedure B employs an M-mode wall echo-tracking diameter measurement system (Wall Track System II, Pie Medical, Maastricht, Netherlands).

V. Results

The results of a single study appear in Figure 4. These data were obtained from a 30 year old male.

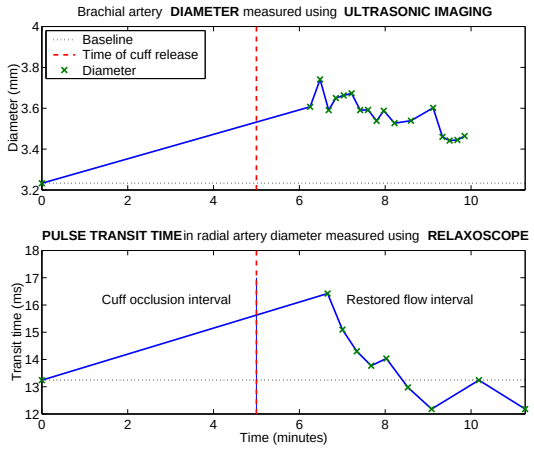

Figure 4: Upon cuff release at $t = 5$ minutes, after a five minute occlusion, PTT rises markedly compared to baseline. It then begins to decrease. A similarity between the time-courses of the PTT (measured using Procedure A) and brachial artery diameter (measured in Procedure B) is apparent.

Similar response time courses have been observed among the five subjects evaluated so far in this ongoing preliminary study. Figure 5 illustrates the maximum percentage changes in diameter and PTT for five subjects.

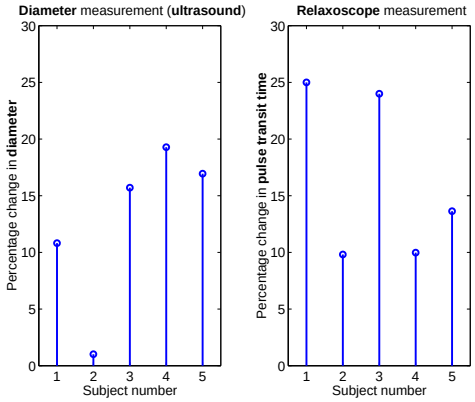

Figure 5: Maximum percentage changes in diameter (left) and PTT (right) after restoration of fbw after 5 minutes of occlusion in 5 subjects.

VI. Discussion

The relaxoscope has the potential to offer a simple low-cost means of non-invasive evaluation of endothelial function that is more sensitive than methods based on brachial artery diameter measurements.

The current human subject evaluation protocol is insufficient to decisively demonstrate the performance of

the relaxoscope. It is especially difficult to evaluate the sensitivity of the relaxoscope to FMVR through comparison with brachial artery diameter measurement owing to the high variability of the latter technique and the unknown variability of the relaxoscope PTT estimate. A protocol involving the administration of agents such as sodium nitroprusside or nitroglycerin that are known to relax arterial walls would be a more effective approach. However, among the five young subjects examined so far under the present protocol, all exhibited increased posthyperemic PTT. This is suggestive of intact endothelial function typical of individuals with no cardiovascular risk factors in this age group. Repeatability studies are required to reinforce these observations, but they are consistent with the underlying physics of vasorelaxation.

In contrast to ultrasonic imaging methods, the relaxoscope does not require precise transducer positioning and the attendant skills of an experienced ultrasound technician. This greater ease of use reduces the significant measurement error that is easily introduced into FMD measurements by slight movements of the subject under examination. The relaxoscope may also be manufactured for under $5,000, or approximately one fifteenth of the cost of an ultrasonic imager.

REFERENCES

[1] D. S. Celermajer, K. E. Sorensen, V. M. Gooch, D. J. Spiegelhalter, O. I. Miller, I. D. Sullivan, J. K. Lloyd, and J. E. Deanfield, "Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis," *The Lancet*, vol. 340, pp. 1111–1115, November 1992.

[2] H. Yasue, K. Matsuyama, K. Matsuyama, K. Okumura, Y. Morikami, and H. Ogawa, "Responses of angiographically normal human coronary arteries to intracoronary injection of acetylcholine by age and segment: Possible role of early atheroscelrosis," *Circulation*, vol. 81, pp. 482–490, 1990.

[3] A. Zeiher, H. Drexler, H. Wollschäger, and H. Just, "Modulation of coronary vasodilator tone in humans: Progressive endothelial dysfunction with different early stages of coronary atherosclerosis," *Circulation*, vol. 83, pp. 391–401, 1991.

[4] J. McLenachan, J. Vita, R. Fish, C. Treasure, D. Cox, P. Ganz, and A. P. Selwyn, "Early evidence of endothelial vasodilator dysfunction at coronary branch points," *Circulation*, vol. 82, pp. 1169–1173, 1990.

[5] D. A. Cox, J. A. Vita, C. B. Treasure, R. D. Fish, R. W. Alexander, P. Ganz, and A. P. Selwyn, "Athreosclerosis impairs flow-mediated dilation of coronary arteries in humans," *Circulation*, vol. 80, pp. 458–465, Sept. 1989.

[6] J. Vita, C. Treasure, G. Nabel, J. McLenachan, R. Fish, A. Yeung, V. Vekshtein, A. Selwyn, and P. Ganz, "The coronary vasodilator response to acetylcholine relates to risk factors for coronary artery disease," *Circulation*, vol. 81, pp. 491–497, 1990.

[7] R. Ross, "The pathogenesis of artherosclerosis: a perspective for the 1990s," *Nature*, vol. 362, pp. 801–9, 1993.

[8] K. E. Sorensen, D. S. Celermajer, D. Geogakopoulos, G. Hatcher, D. J. Betteridge, and J. E. Deanfield, "Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein (a) level," *Journal of Clinical Investigation*, vol. 93, pp. 50–55, Jan. 1994.

[9] M. Williams, W. Sutherland, M. McCormick, S. de Jong, and R. Walker, "Impaired endothelial function following a meal rich in used cooking fat," *Journal of the American College of Cardiology*, vol. 33, pp. 1050–5, Mar. 1999.

[10] D. Celermajer, K. Sorensen, C. Bull, J. Robinson, and J. Deanfield, "Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction," *Journal of the American College of Cardiology*, vol. 24, pp. 1468–74, November 1994.

[11] T. Neunteufl, S. Heher, R. Katzenschlager, G. Wolfl, K. Kostner, G. Maurer, and F. Weidinger, "Late prognostic value of flow-mediated dilation in the brachial artery of patients with chest pain," *American Journal of Cardiology*, vol. 86, no. 2, pp. 207–10, 2000.

[12] R. M. Krauss, R. H. Eckel, B. Howard, L. J. Appel, S. R. Daniels, R. J. Deckelbaum, J. W. Erdman, P. Kris-Etherton, I. J. Goldberg, T. A. Kotchen, A. H. Lichtenstein, W. E. Mitch, R. Mullis, K. Robinson, J. Wylie-Rosett, S. S. Jeor, J. Suttie, D. L. Tribble, and T. L. Bazzarre, "AHA dietary guidelines: revision 2000: A statement for healthcare professionals from the nutrition committee of the American Heart Association," *Circulation*, vol. 102, pp. 2284–2299, Oct 2000.

[13] Y. Higashi, S. Sasaki, S. Kurisu, A. Yoshimizu, N. Sasaki, H. Matsuura, G. Kajiyama, and T. Oshima, "Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide," *Circulation*, vol. 100, pp. 1194–1202, Sep 1999.

[14] K. E. Sorensen, D. S. Celermajer, D. J. Spiegelhalter, D. Georgakopoulos, J. Robinson, O. Thomas, and J. E. Deanfield, "Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility," *Br Heart J*, vol. 74, pp. 247–253, Sep 1995.

[15] T. C. Andrews, E. J. Whitney, G. Green, R. Kalenian, and B. E. Personius, "Effect of gemfibrozil +/- niacin +/- cholestyramine on endothelial function in patients with serum low-density lipoprotein cholesterol levels $<$160 mg/dl and high-density lipoprotein cholesterol levels $<$40 mg/dl," *Am J Cardiol*, vol. 80, pp. 831–835, Oct 1997.

[16] K. L. Hardie, S. Kinlay, D. B. Hardy, J. Wlodarczyk, J. S. Silberberg, and P. J. Fletcher, "Reproducibility of brachial ultrasonography and flow-mediated dilatation (fmd) for assessing endothelial function," *Aust N Z J Med*, vol. 27, pp. 649–652, Dec 1997.

[17] N. M. de Roos, M. L. Bots, and M. B. Katan, "Replacement of dietary saturated fatty acids by *trans* fatty acids lowers serum HDL cholesterol and impairs endothelial function in healthy men and women," *Atherosclerosis, thrombosis and vascular biology*, vol. 21, pp. 1233–1237, 2001.

[18] W. Nichols and M. O'Rourke, *McDonald's blood flow in arteries, 4th ed.* Edward Arnold, 1998.

[19] M. Anliker, M. B. Histand, and E. Ogden, "Dispersion and attenuation of small artificial pressure waves in the canine aorta," *Circulation Research*, vol. 23, pp. 539–551, Oct. 1968.

[20] M. Landowne, "A method using induced waves to study pressure propagation in human arteries," *Circulation Research*, vol. 5, pp. 594–601, Nov. 1957.

[21] U. Dinnar, *Cardiovascular Fluid Dynamics*. CRC Press, 1981.